D 1 6. (Amended) A method according to claim 1 wherein said individual is a human.

REMARKS

The presently claimed invention offers novel and nonobvious methods for treating individuals with diabetes mellitus by inhibiting the interaction between the cAMP responsive transcriptional activator CREB and CBP, a protein that binds to the phosphorylated (i.e., activated) form of CREB and mediates cAMP responsive transcription. Also provided are methods to select such inhibitors.

Claims 1-7, 12 and 17 are pending in the case. Claim 6 has been amended herein to define Applicant's invention with greater particularity. The amendments to the claim are shown in the attached document titled "CLAIMS WITH MARKINGS TO SHOW CHANGES MADE" (EXHIBIT A). Support for the claim amendment is found throughout the specification. The amendment raises no issue of new matter and entry is respectfully requested.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The rejection of claim 6 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for lacking antecedent basis in claim 1 is respectfully traversed. The rejection has been obviated herein by amendment of claim 6. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The rejection of the claims under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement is respectfully traversed. As will be detailed below, all of the reasons on which the rejection is based are without merit. Accordingly, the rejection fails to state a prima facie case for lack of enablement or, alternatively, the rejection has been rebutted by Applicant's arguments to the contrary.

A. The Evidence cited by the Examiner does not Constitute a Prima Facie Rejection for Lack of Enablement.

Under Patent Office practice, a patent specification is considered to be in compliance with the enabling requirement of § 112, first paragraph, unless there is reason to doubt the objective truth of the statements contained therein. Thus, the examiner carries the initial burden to substantiate a rejection for lack of enablement. *In re Marzocchi,* 439 F.2d 220, 223-24 (CCPA 1971). In accordance with the burden, the Patent Office must explain why the truth or accuracy of any statement in the specification is doubted and "back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *Id.; see also, In re Richard Sichert,* 566 F2.d 1154, 1161 (CCPA 1977)) ("The PTO has cited to no evidence or reference that contradicts or is inconsistent with any supporting statement of the disclosure.").

As will be shown below, none of the reasons offered by the Examiner lend support to a prima facie rejection for non-enablement.

1) The Examiner's Position that Enablement Requires the Art to Demonstrate (as of Applicant's filing date) that Applicant's Mechanism of Action for Treating Diabetes was Known is Without Basis in the Law and, is Unsupported in any Event.

It is respectfully submitted that there in nothing in the patent statute which requires that the mechanism of action of an invention be demonstrated in the art as of the patent application filing date for enablement to be present. In fact, any such rule would be against the public policy underlying the statute because its impact would be to bar original discoveries based on new mechanisms of treatment. On the contrary, it is the Examiner's burden to set forth evidence that questions the objective enablement provided in Applicant's disclosure. No such evidence has been offered by the Examiner.

2) The Fact that Applicant's method or mechanism of action is not discussed in Merck Manual is NOT Relevant to the Question of Enablement.

Applicant respectfully disagrees with the Examiner's assertion that the enablement rejection is supported by the fact that Applicant's method of treatment is not discussed in the section of the Merck Manual, 17th edition, that addresses treatment of diabetes (citing the Merck Manual pages 174-176). Such evidence would only be relevant to the question of enablement if it would be shown that the Merck Manual is a reliable source for the latest in diabetes treatment methods and mechanisms of action. The Examiner has the burden to provide this essential evidence for relevance but has offered nothing.

Although Applicant has no duty to cite contrary evidence on this account since the Examiner has the burden, and the Examiner's assertion remains unsubstantiated, Applicant respectfully submits that the Merck Manual is not probative evidence of non-enablement. The Merck Manual discusses well established methods of diabetes treatment, mainly treatment using insulin, sulfonylureas, and certain anti-hyperglycemic drugs; The Manual, however, is silent as to new methods of diabetes treatment as evidenced by its failure to mention any of a larger number of recently patented diabetes treatment methods (a search for "diabetes," "treat" and "method" as claim terms identified 89 issued U.S. patents; a random sampling of these showed that many are directed to new methods of diabetes treatment that are not mentioned in the Merck Manual) (See e.g., U.S. No. 6,323,314 – thiophene derivatives; U.S. No. 6,300,349 N-substituted 2(1H) pyridones; U.S. No. 5,888,507 – antibody to VLA-4; U.S. No. 5,834,032 – zinc cation, anion and cyclo-Hisporo; U.S. Nos. 6,146,653 - amylin agent; U.S. No. 5,541,192 substituted sulfonamides; U.S. No. 5,691,386 - triterpenoids; 5,674,900 - terpenoids, U.S. No. 5,700,795 -muscarinic receptor antagonists; and U.S. No. 5,561,110 - carnosine).

Accordingly, failure to be discussed in the Merck Manual is a fact entirely without moment to the present rejection and cannot be used by the Examiner to support a prima facie rejection for enablement.

3) The Mayr and Herzig References Do Not Support the Rejection.

Mayr et al. ("Transcriptional Regulation of the Phorphorylation-Dependent Factor CREB" Molec. Cell Biol., 2:599, 2001) and Herzig et al. ("CREB Regulates Hepatic Gluconeogenesis Through the Coactivator PGC-1" Nature 413:179-183, 2001), both of record in the case, do not support the rejection for lack of enablement as alleged. Rather, these articles provide additional evidence that the claimed invention is enabled as described.

Mayr et al. (Mayr) is a review article published in the prestigious journal, Nature. Mayr makes clear in the Abstract to the article that CREB is involved in control of glucose levels. Mayr, p. 599 (stating that CREB "functions in glucose homeostasis; emphasis added). Mayr also describes that the mechanism by which CREB controls glucose homeostasis involves phosphorylation of CREB at Ser133, which promotes complexing with the transcriptional co-activator CBP. Mayr, p599, left column and Figure 1a. These conclusions are consistent with Applicant's disclosure teaching involvement of CREB-CBP complex in diabetes. Furthermore, Herzig et al. ("Herzig") reported that CREB controls glucose homeostasis through expression of gluconeogenic enzymes via the transactivator, PGC-1. Herzig also used normal and diabetic animals to prove that a reduced CREB activity causes fasting hyperglycemia *in vivo*, a result that Herzig states "is correlated with Type II diabetes." Herzig, page 179 (Abstract; emphasis added).

Therefore, both the Mayr and Herzig articles support enablement of Applicant's disclosure. The Examiner's position to the contrary is not supported by any scientific reasoning. Furthermore, the Examiner has cited to nothing of consequence in Mayr or Herzig which supports this alleged lack of enablement.[1] Accordingly, a prima facie case

[1] The Examiner's reliance on Herzig as allegedly supporting the rejection based on a single sentence referring to treating diabetes (p. 182), is without support; it is contrary to the disclosure as a whole which teaches that CREB is central to glucose homeostasis and, moreover, ignores the context in which the statement is made.

for lack of enablement cannot be based or otherwise supported by the Mayr or Herzig disclosures.

4) The Rejection Fails to Raise Any Scientific Reasoning For Why Applicant's Method is not Enabled as Described.

The Examiner has offered no acceptable evidence or reasoning (scientific or otherwise) that is inconsistent with the Applicant's method for treating diabetes by administering a compound that inhibits binding of CREB to CPB. There also is no support for the Examiner's assertion that the specification lacks factual evidence supporting enablement including a working example that a compound that inhibits or disrupts the binding of CREB or CPB provides any beneficial effect in treating diabetes mellitus. The Examiner admits that the specification provides an enabling method for identifying a compound that inhibits CREB-CPB interaction, and Applicant further points out that the specification provides substantial guidance in compound formulation and in vivo dosage (see pages 19-20). Although Applicant's disclosure does not include in vivo experimental data, there is no per se requirement to have human clinical data to enable a method of therapy. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993) ("[I]t is irrelevant whether the teaching of the patent is provided through broad terminology or illustrative examples"). The specification is presumed to be enabling and the Examiner has failed to meet his/her burden to set forth credible reasoning for why inhibitory compounds selected by Applicant's method would not be useful in treating diabetes.

In view of the above, it is respectfully submitted that the Office Action fails to state a prima facie rejection because it is not founded on sufficiently "acceptable evidence or reasoning which is inconsistent" with the Applicant's method. *In re Marzocchi,* 439 F.2d 220, at 223-24 (CCPA 1971). Accordingly, the Examiner is respectfully urged to withdraw the rejection and allow the claims.

B. Assuming *Arguendo* that a Prima Facie Rejection for Enablement has been Stated, the Facts of Record Overcome the Rejection.

The Examiner carries the initial burden to state a prima facie rejection for enablement, but once that is done, the burden shifts to applicant to rebut this conclusion by presenting evidence to prove that the disclosure in the specification is in fact enabling. *In re Eynde*, 480 F.2d 1364, 1376 (CCPA 1973). Materials submitted to prove enablement must be factual evidence such as patents, publications and affidavits. *Id.* References published after the filing date of the application in question may be used in this regard if the purpose is to prove the accuracy of a statement in the specification. *See In re Marzocchi*, 439 F.2d at 224, n.4.

Although it is respectfully submitted that the Examiner has not met his/her burden, even if one assumes *arguendo* that such burden has been met, the evidence of record in any event is more than sufficient to prove that the specification is enabling. As admitted by the Examiner, the specification teaches methods to identify a compound that inhibits the interaction of CREB with CBP. Included is a description of various cell lines to use and expression vectors to express the interacting proteins in the form of a functional bioassay. Inhibiting compounds are described and include, for example, fragments of CREB or CBP, or antibodies that bind to epitopes of CREB or CBP that are involved in the interaction (see page 13-15). The working examples of the specification provide further enabling support for compound selection methods. With respect to diabetes treatment, for compounds which meet the inventors' criteria, the specification provides a general description of suitable routes of administration, methods of formulation, and dosing, the latter including concentration ranges (page 17-18).

To further support Applicant's position that the description in the specification is indeed, enabling, Applicant cites to peer reviewed scientific publications. As discussed above, Mayr demonstrates that CBP/CREB interaction is required to transcriptionally activate CREB, while Herzig demonstrates that transcriptionally activated CREB is involved in diabetes mellitus. The Mayr and Herzig articles, published in peer-reviewed and

prestigious scientific journals, strongly evidence that Applicant's patent disclosure is enabling and overcomes any alleged suggestions to the contrary, such as the failure to be mentioned in the Merck Manual. The Examiner's failure to consider these references as evidence because they were published after the filing date of the instant patent application and use methods to obtain results that go beyond those instantly disclosed is without basis in the law. These references are relied on to prove the truth of statements in Applicant's disclosure that disruption of CREB-CBP interaction can be used to treat diabetes rather than to supplement the disclosure itself. *See In re Marzocchi,* 439 F.2d at 224, n.4 (indicating that references which are not prior art can be used to rebut a prima facie case for lack of enablement if the "question would be regarding the accuracy of a statement in the specification, not whether that statement had been made before.").

In view of the above, it is respectfully submitted that even assuming *arguendo* that a prima facie case has been stated by the Examiner, such case is rebutted by scientific reasoning and other evidence provided by Applicant. Accordingly, the Examiner is respectfully urged to withdraw the rejection and allow the claims.

SUMMARY

It is respectfully submitted that the above amendments and remarks place the application in condition for allowance. Accordingly, reconsideration and favorable action on all the claims is respectfully requested. If any matters remain to be resolved, the Examiner is invited to contact the undersigned at the telephone number set forth below so that a prompt disposition of this application can be achieved.

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(088802-2753)

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-0872**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Date: April 17, 2002

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Enclosures: Appendix A

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(088802-2753)

APPENDIX A: CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

6. (Amended) A method according to claim 1 wherein said [~~biological system is an intact organism~~] individual is a human.